*Introduction*

Advantages and pitfalls of chemotherapy and radiotherapy as complementary treatment modalities in operable non-metastatic esophageal and gastric junction adenocarcinoma have been fiercely debated in recent years. Advocates of systemic therapy among the medical oncology community argue that multi-agent chemotherapy should be favoured due to competing risk of micrometastatic dissemination in patients achieving primary tumor eradication by surgery. On the other hand, radiation oncologists vocally support the use of chemoradiation as a critical component of the therapeutic management in combination with surgery, showing an acceptable toxicity profile, high treatment completion and clear-margin resection rates, as well as promising survival outcomes. In selected patients, a watch-and-wait strategy with omission of surgery could also be envisioned [esostrate].

Interestingly a similar heated debate died down during the last decade for gastric adenocarcinoma (GC), following advancement in surgical technique and publication of major trials that failed to prove an additional benefit of chemoradiation in patients eligible to receive perioperative chemotherapy and surgery. Insights into the molecular landscapes of gastric cancer could provide a roadmap to assist with patient section and stratification, and rationally designed trials when combining radiation with targeted therapies The aim of this review is to critically analyse current evidence in the perioperative management of GC and to address possible strategies to implement the use of chemoradiotherapy in the light of novel advances in treatment technique.

*Landmark trials- to me the advances in surgery and the integration of D2 nodal resection are key when considering the use of radiotherapy*

Intergroup 0116 evaluated the use of surgery followed by adjuvant chemoradiotherapy versus exclusive surgery in gastric adenocarcinoma patients (AJCC T≥3 and/or node positive). In this phase III trial, 559 patients were randomized between 45 Gy postoperative radiotherapy with concurrent 5FU versus observation following R0 gastrectomy [11547741,22585691]. At 10-year follow-up, a benefit of chemoradiotherapy was observed on both overall survival (36 months versus 20 months, HR: 1.3) and disease-free survival (30 months versus 19 months, HR: 1.5). At subset analysis, reported benefit was limited to non-diffuse adenocarcinoma subtype. Toxicity data were reported only for the experimental arm, showing high incidence of Grade 3 events (54% and 33% for hematologic and gastrointestinal side effects, respectively) for whom

**Commented [MH1]:** In my view this trial is not relevant anymore- the only reason it was positive was that RT was making up for bad surgery, also the RT was old fashioned - 2D

no comparison with the observation arm was provided in the final publication. However, a G5 event rate <1% was reported, indirectly suggesting no additional treatment-related mortality in patients receiving adjuvant chemoradiation. For these reasons, postoperative chemoradiation was promptly integrated in US treatment guidelines.

Historically, no benefit has been highlighted for adjuvant chemotherapy in the setting of operated gastric cancer (GC) in the last century [8336183]. For this reason, a perioperative chemotherapy approach was proposed in the early 2000s in Europe and was tested in the UK randomized controlled MAGIC phase III trial [16822992]. Five hundred tree operated GC patients (AJCC T≥2 and/or node positive) were included in the study and allocated to exclusive surgery or to perioperative surgery with 3 preoperative cycles and 3 postoperative cycles of chemotherapy using the ECF (Epirubicin, Cyclophosphamide, 5-Fluoro Uracil) regimen. At a median follow-up of 4 years, a significant benefit in terms of 3-years DFS (40% versus 25%, HR 0.66) and 3-year OS (36% versus 23%, HR 0.74) was reported. Furthermore, a significant impact on tumor downstaging was observed with decreased tumor size in the experimental arm versus control arm (median 3 cm vs 5 cm). However, an imbalance in tumor stage and nodal involvement at randomization favoring the chemotherapy arm was acknowledged. Finally, similar incidence of G3 toxicity between the two arms was reported. Following publication of the MAGIC, perioperative chemotherapy became the preferred treatment modality in Europe.

At the same time, in North America, an approach including chemotherapy intensification in patients receiving chemoradiation was explored in the CALGB 80101 phase III trial [28976791]. Patients receiving surgery and adjuvant chemoradiation were randomized between perioperative chemotherapy with Leucovorin-5-Fluorouracil versus ECF. At a median follow-up of 6.5 years, no superiority in terms of 5-year OS (44% versus 44%) and DFS (39% versus 37%) rates was demonstrated. Most interestingly, chemotherapy intensification with ECF was not associated with decreased incidence of distant metastases and was burdened by a higher treatment discontinuation rate (24% vs 13%).

However, comparison with surgical series from Japan and Korea questioned the results of these trials. Interestingly, surgical management of GC in Eastern countries included a more aggressive nodal dissection approach beyond perigastric nodal drainages as performed in Western countries (D1 dissection) and encompassed the coeliac axis and possibly pancreatectomy/splenectomy according to tumor location (D2 dissection), aiming a minimum of 15 lymph nodes sampled in the surgical specimen. Since the value of this approach was questioned in Europe due to potential increased mortality and morbidity, a D2 resection was

under-represented in the above cited trials: 10%, 41%, and 55% in Intergroup 0116, MAGIC, and CALGB 80101 trials, respectively. To clarify this issue, the Dutch group performed the DCGT D1-D2 trial, showing, in 711 GC patients treated with curative intent, that D2 versus D1 dissection was associated, at a median follow up of 15 years, with improved cancer-specific survival (48% versus 37%) and local control (22% vs 12%), without significant difference in terms of distant metastatic recurrence and overall survival [20409751]. To explain the lack of difference in overall survival despite improved cancer-related mortality, a higher mortality and surgical complication rate was put forward that could be reduced with omission of prophylactic splenectomy/pancreatectomy (D1+). Following implementation of the surgical management in light of the DCGT D1-D2 trial, a nation-wide improvement in adjusted 5-year OS was observed, raising from 34% to 42% in the post-trial era [19144490].

Following results of the DCGT D1-D2, the value of adjuvant treatment in patients receiving a more comprehensive surgical approach was questioned. A pooled analysis including patients from a prospective phase II trial of adjuvant chemoradiation and from DCGT D1-D2 showed that a LRFS benefit of chemoradiation was restricted to patients receiving D1 (2% versus 8%) but not D2: no difference in survival was also shown after adjustment for the Maruyama Index [20368551]. A benefit of chemoradiation was also reported in case of R1 resection, resulting in decreased local recurrence rate (6% versus 26%, p=0.002) and improved survival (66% versus 2%, p=0.02).

In terms of improving locoregional outcomes adjuvant CRT in the “era of D2 resection” should be considered in patients where a D2 resection could not be undertaken and microscopically positive disease.

*Modern trials informing current clinical practice (ARTIST and CRITICS)*

To address this issue, prospective randomized trials were started in Europe and Asia. ARTIST was a Korean phase III trial including 458 GC patients treated with D2 dissection who received perioperative chemotherapy (Cisplatin-Capecitabin for 3 preoperative and 3 postoperative cycles) versus integrated perioperative chemotherapy with adjuvant chemoradiation (Cisplatin-Xeloda for 2 preoperative cycles, adjuvant 45 Gy chemoradiation with Capecitabine and 2 postoperative chemotherapy cycles) [25559811, 22184384]. No difference in both DFS and OS was observed. However, at subset analysis, an impact on 3-year DFS was observed in patients with lymph node involvement (77.5% versus 72.3%, p=0.04). Following results from

ARTIST, ARTIST-2 was planned to include only GC patients with positive nodal staging after D2 dissection randomized between three arms: a) perioperative oral chemotherapy with S1 for 4 preoperative and 4 postoperative cycles; b) perioperative chemotherapy with S1-Oxaliplatin for 4 preoperative and 4 postoperative cycles; c) perioperative chemotherapy with S1-Oxaliplatin for 2 preoperative cycles, 45 Gy adjuvant chemoradiation with S1 followed by 2 postoperative chemotherapy cycles [33278599]. The study failed its accrual target of 855 participants and was interrupted for futility of S1 alone after recruiting 546 patients, thus was not powered to highlight differences in DFS (primary endpoint) between the other 2 arms. However, at study closure, no difference in terms of DFS was shown in favor of adjunction of chemoradiation.

In Europe, the CRITICS phase III compared perioperative chemotherapy with ECF according to the MAGIC regimen versus preoperative ECF for 3 cycles and adjuvant 45 Gy chemoradiation with Cisplatin and Capecitabin [29650363]. The study included 788 GC operated patients with mostly D1+/D2 dissection (87%). Again, no difference was found in terms of OS and DFS between the two arms, with similar G≥3 toxicity profile. **Table 1** summarizes results from major trials discussed in this review.

The worse outcomes in the CRT arm in the CRITICS study were driven by the recurrence of the disease in the peritoneum only, highlighting the need for markers to identify those who are at risk of peritoneal disease.

Moreover, interest toward perioperative chemotherapy was raised following the recent publication of the FLOT4 trial [30982686]. In this phase III study, including 716 GC patients (AJCC T≥2 and/or node positive), perioperative chemotherapy with ECF was compared with a more intensive schedule (5-FU, Leucovorin, Oxaliplatin, Docetaxel, FLOT) that showed an indisputable benefit in favor of the experimental regimen resulting in longer median OS (50 months versus 30 months, HR 0.77) and DFS (30 months versus 18 months, HR 0.75) , although at the price of a non-negligible rate of G≥3 events (27%) requiring hospitalization in 25% of cases.

In the end, promising results from FLOT4 and disappointing data from CRITICS, ARTIST, and ARTIST-2 shifted the balance in favor of the perioperative chemotherapy approach, that became the recommended treatment modality according to the European Society of Medical Oncology guidelines [35914639]. Consequently, an ancillary role of adjuvant chemoradiation was acknowledged only in limited clinical circumstances such as D1 nodal dissection or R1 margin status.

*Rethinking the balance*

Despite the silent demise of radiotherapy from clinical recommendations and treatment guidelines in GC in Europe and Japan , a number of critical issues should be addressed.

In first place, we should consider the balance between survival benefit and toxicity profile of perioperative chemotherapy. Treatment intensification with FLOT compared to ECF comes at the price of both restricted access to effective regimens (since a significant proportion of patients may be judged unfit for this protocol due to age and performance status), and increased risk of treatment-related toxicity requiring medical intervention, thus possibly increasing the delay to surgery in case of severe adverse events. On the other hand, while promising, long term survival with FLOT is still burdened by an estimated 43% mortality rate at 5 years that require further improvement, although no further treatment escalation with traditional cytotoxic agents can be safely envisioned.

Secondarily, when we examine current literature on both perioperative chemotherapy and adjuvant chemoradiotherapy, we should carefully acknowledge the scarce compliance to medical treatments in the postoperative phase, since less than half of patients are able to receive the whole treatment sequence. For instance, in CRITICS trial, adjuvant chemoradiation and postoperative chemotherapy were fully administered in 50% and 46% of patients, respectively. Similarly, in the FLOT4 trial, only 43% of patients completed the three postoperative cycles, and in the real life setting this figure can go as low as <20% according to an Italian multicentric study (REALFLOT) [34625033]. This observation stresses the need to anticipate as much as possible non-surgical treatment in the neoadjuvant phase, including the option of preoperative radiotherapy that was not considered in the above-mentioned trials. It should be noted that an early phase III trial of neoadjuvant chemotherapy (EORTC 40954) versus surgery alone did not show a survival benefit with D2 resection, suggesting the need for an adjuvant phase treatment in patients treated with chemotherapy [21060024].

Finally, we should carefully examine the data of major phase III clinical trials cited above and consider that in all cases, no formal superiority of perioperative chemotherapy on postoperative chemoradiation have been proven so far. Indeed, in all cases, no difference in term of outcome has been demonstrated for one treatment modality over the other. Most importantly, in all these trials, the futility of radiotherapy has been stated indirectly due to lack of additional benefit of the integration of adjuvant chemoradiation with a perioperative chemotherapy schedule. This

observation, together with the observed low rate of treatment completion in patients eligible for adjuvant chemoradiation, suggest that current evidence do not legitimate an inferiority of chemoradiation compared to perioperative chemotherapy, but rather demonstrate an inability to efficaciously integrate chemotherapy and radiotherapy to obtain a synergistic effect. We should also consider that European trials such as CRITICS tested a combination of chemoradiotherapy with Epirubicin-based chemotherapy, that has been questioned before FLOT4 following limited antitumor activity of Epirubicin in the UK MRC OE05 trial [28784312, 28129519].

*Perioperative chemotherapy versus neoadjuvant chemoradiation: terms and conditions*

While chemoradiation has been traditionally relegated to the postoperative setting, preoperative treatment might represent the most logic choice. The potential benefits of a preoperative management include:

- Increased compliance rate in treatment-naïve patients
- Improved treatment volume delineation due to integrity of anatomical landmarks, and better reproducibility
- Possibility of tumor downstaging and determination of pathologic response, that may guide clinical decision for further adjuvant treatment.
- Prevention of tumor cell spillage in the surgical bed.

This approach in gastric cancer was tested in the landmark phase II trial RTOG 9904. In this study, 43 gastric cancer patients received a multimodal management consisting of two cycles of induction chemotherapy with Cisplatin/5-FU and a 45 Gy conventionally fractionated chemoradiotherapy, followed by surgical intervention (D2 dissection in 50% of cases) at 6 weeks. Interestingly, with a median survival of 33 months, patients achieving pCR (26% of patients) showed longer survival [16921048].

However, comparative randomized data between preoperative chemoradiation and perioperative chemotherapy in gastric cancer are lacking. Currently, the only phase III trial that prospectively compared perioperative chemotherapy and preoperative chemoradiation in distal esophageal and oesophago-gastric junction is the NEO-Aegis trial [37734399].

While this trial has been widely criticized for early closure during the COVID-19 pandemic despite having reached the threshold number of events based on sample calculation, its main

criticism was based on seldom use of FLOT in the perioperative chemotherapy cohort compared to ECF since accrual started before the study by Al-Batran. Therefore, despite a prompt amendment of the protocol in 2018, only 18% of patients received FLOT in the intention-to-treat population.

Nonetheless, it should be noted that, despite the use of an outdated chemotherapy regimen in most patients, outcomes in the perioperative chemotherapy were in line with the results of the FLOT4 study, showing a median OS and DFS of 50 and 30 months, respectively. Interestingly, no difference in the occurrence of distant metastasis was shown between the 2 arms, despite common sense suggesting that a triple agent chemotherapy should be more efficient in eradicating micrometastasis compared to a merely radiosensitizing regimen such as Carboplatin-Paclitaxel. Most notably, a statistically significant difference was highlighted in favor of the CROSS arm in terms of pathological complete response (pCR) and clear margin (R0) resection: 12% versus 4% and 96% versus 82%, respectively.

It should be noted that higher rates of pCR and R0 resection in patients receiving chemoradiation have been shown in previous prospective studies randomizing esophageal and esophago-gastric junction carcinomas, as well as similar survival outcomes and patterns of recurrence. In the NEORes-1 study, addition of radiotherapy (40 Gy/2 Gy per fraction) to three-weekly Cisplatin/5-FU resulted in improved R0 (87% versus 74%) and pCR rates (28% vs 9%) in advanced adenocarcinoma and squamous cell carcinoma [30137281]. In the POET trial, enrolling oesophago-gastric junction adenocarcinomas, a significant benefit in terms of pCR (96% vs 85%) and a trend toward improved survival was observed in patients receiving induction chemotherapy plus radiotherapy versus chemotherapy alone [28628843]. However, only 126 patients were included instead of the 354 planned. While it could be argued that results from trials including mainly oesophageal cancer patients may explain the difference in terms of response to treatment, a large retrospective database from the NCDB focusing only on GC treated with surgery either after chemoradiotherapy or chemotherapy confirmed a higher incidence of pCR (17% vs 6%) and R0 resection (92% vs 86%) in patients treated with chemoradiotherapy [29730720]. However, conversely with RTOG 9904, none of these studies demonstrated a clear correlation between improved pCR and survival. A recent comparative analysis from the NCDB showed that, in a large cohort of patients receiving neoadjuvant treatment for gastric cancer, OS was superior in patients receiving perioperative chemotherapy despite significantly higher pCR and R0 resection rates in patients receiving preoperative chemoradiation [37986548].

Results from the ongoing ESOPEC trial, testing CROSS versus FLOT are eagerly awaited to clarify this issue in esophago-gastric cancers.

Most importantly, two prospective randomized trials are currently testing preoperative chemoradiation and perioperative chemotherapy in gastric cancer.

First, TOPGEAR is a phase III trial testing, in 574 gastric cancer patients, preoperative chemoradiation (45 Gy+5FU) with a perioperative chemotherapy regimen consisting of ECF or FLOT after protocol amendment in 2018 [28337660]. The interim analysis showed that 92% received the planned chemoradiation course. Interestingly, no difference in surgical morbidity (22%) and overall toxicity was reported. Final results are waited for the end of 2024.

Secondarily, the CRITICS-II study is currently assessing, in a three-arm phase II design, the use of preoperative chemotherapy (Docetaxel-Oxaliplatin-Capecitabin alone) with or without CROSS chemoradiation versus CROSS in operable patients following staging laparoscopy [30200910]. Target accrual was reached in 2024.

*Empowering radiotherapy: synergistic systemic treatments*

Commented [MH2]: Replaced with systemic treatments as these include immune, targeted therapies and chemotherapy

Deleted: *chemotherapy*

While results from CRITICS-II and TOP-GEAR may provide critical data to establish the role of preoperative chemoradiation in the management of resectable gastric cancer, it should be noted that both treatment strategies are centred on the use of traditional antiblastic chemotherapy:

1) Concurrently, as radiosensitizing agents to increase the local effect of radiotherapy
2) Sequentially integrated in a multimodal treatment (in the induction or adjuvant phase), under the assumption that systemic treatments schedules that proved active in this setting may achieve a "spatial cooperation" with radiotherapy, thus reducing the risk of distant dissemination

Deleted: chemotherapy

However, as shown in previous experiences reported in this article, a synergistic effect of chemoradiation with chemotherapy was not demonstrated so far and may potentially result in severe additional toxicity. It could be argued that, if preoperative chemoradiation is proposed as an alternative option, novel treatment combinations should be explored to enhance the effect of chemoradiation while maintaining an acceptable toxicity profile. In particular, Immune Checkpoint Inhibition (ICI) has been tested in association with radiotherapy based on the immune modulating effect of ionizing radiation in the tumor microenvironment, as observed in other settings such as locally advanced non-small cell lung cancer [28885881]. The Phase III

CheckMate 577 study tested adjuvant immunotherapy with Nivolumab in 794 resected oesophageal cancer patients (71% adenocarcinoma) who did not achieve complete pathological response after preoperative chemoradiation with CROSS [33789008]. While overall survival results are pending, a significant benefit in its primary endpoint of disease-free survival was observed (22 months versus 11 months), irrespectively of PD-L1 expression. Interestingly, a similar strategy involving the combination of ICI (Pembrolizumab) with FLOT was tested in the phase III Keynote-585, that was closed to accrual after futility analysis due to lack of event-free survival benefit compared to chemotherapy alone [38134948].

Another phase II trial (NEOplanet) tested preoperative chemoradiation in association with neoadjuvant ICI with Camrelizumab, achieving its pre-specified endpoint of pCR (33%), with an acceptable safety profile [36357415]. Chemoradiation with ICI may represent a promising area of investigation, although larger trials are needed to assess its added value in the treatment sequence. Furthermore, novel agents specifically designed for combinational use with radiotherapy are currently under development. Xevinapant, an inhibitor of IAPs (Inhibitors of apoptosis proteins), a class of apoptosis regulators that increase the resistance of cancer cells to apoptosis, has been recently tested in association with radiotherapy for locally advanced head and neck cancer treated with radical intent, showing a significant benefit in terms long-term survival without additional toxicity [36796234].

*Technical advancements*

In currently available studies on GC radiotherapy, a total dose ranging from 45 to 50 Gy using a conventional 1.8-2 Gy fraction regimen were explored both in the neoadjuvant and adjuvant setting. Even for these bland dose regimens, reported severe toxicity rates (up to 33-54% in the intergroup study and 21% in RTOG 9904) jeopardized the safety of these procedure and negatively affected the completion rate, hence hindering possible further dose escalation. Moreover, treatment interruption due to toxicity may impact locoregional control [24655942]. In the CROSS trial, high compliance to treatment (96%) and a manageable toxicity profile were obtained at the expenses of the delivery of a lower total dose of 41.4 Gy. While this protocol yielded promising results particularly in the preoperative management of oesophageal squamous cell carcinoma, resulting in high rates of surgery omission due to complete clinical response, the target dose may be insufficient to exert a significant clinical activity in radioresistant gastric adenocarcinomas. It is noteworthy that the above cited studies from the

early 2000s recommended a 2D planning technique based on 2 anteroposterior beams, that results obsolete compared to current standard. Modern radiotherapy planning, including CT-based 3D planning and intensity-modulated radiotherapy (IMRT), may result in superior target coverage and healthy tissue sparing, thus potentially enabling for lower toxicity and improved compliance [25241995]. Up-to-date radiotherapy techniques also allow to account and correct tumour and organ displacement during the breathing cycle, a significant source of uncertainty in dose delivery. For instance, in a recent study, substantial reduction in mean abdominal shift (from 11.1, 1.9 and 5.5 to 3.7, 1.6 and 2.8 mm respectively in the craniocaudal, lateral and anteroposterior direction) were obtained using a breath-hold technique to reduce dose to the organs at risk, potentially allowing for dose escalation [22716276]. Interestingly, another source of inaccurate dose delivery is interfractional anatomic variation in the upper abdominal organs, particularly in relation with changes in stomach filling. Daily adaption, generating a new treatment plan according to the anatomy of the day, is an expanding treatment option that has been implemented in particular in the upper abdominal district. Most notably, novel treatment platform combining Magnetic Resonance Imaging and radiotherapy linear accelerators (MRI-Linac) may represent an emerging option to ensure in-treatment tumor targeting due to exquisite contrast on soft tissue, management of intrafraction motion through respiratory gating and daily adaption of interfractional anatomic variation through daily on-line replanning: this could prove particularly beneficial in non-operated gastric cancer patients due to daily changes in gastric volume [37746250].

Another critical aspect is related to the target delineation. At present, no consensual definition of treatment volumes in the postoperative setting has been reached, since most published experiences rely on study protocol from landmark prospective trials and consensus statements [11872272, 18757225]. While there is substantial agreement in the need to include tumor bed, surgical anastomosis, and nodal drainage, substantial interobserver variability in delineation is expected even among experts referring to the same treatment protocol due to the complexity of treatment volume recognition in the postoperative setting and possible differences in surgical technique [19836158]. Moreover, disagreement may exist with the definition of the nodal areas included in the irradiation field that may vary according to tumour location and lymph nodal region classification in use. For these reasons, a preoperative approach based on the intact tumor may improve the identification of treatment volumes both in the delineation phase and in the treatment phase using on-line imaging.

**Commented [MH3]:** Not needed-possible too detailed info

**Commented [MH4]:** If you look at patterns of failure these are outside the d2 field https://doi.org/10.1016/j.radonc.2013.05.025, making the point that RT is not needed in D2 surgery

**Commented [MH5]:** For me the preoperative approach is justified by - ability to complete treatment, Enhance resectability
Assess response in primary tumour
Improve local control
Treat micrometastases early
Immune stimulation...

Target delineation may be also improved by early integration of pretreatment imaging, particularly with the use of simulation 18-FDG PET-CT [29172270] or MRI, particularly if acquired in treatment position. Consensual volume definition may be henceforth more easily obtained. Quality Assurance from the TOPGEAR trial was addressed in a recent publication. After central review, 28% of treatment plans required resubmission due to minor or major protocol violations, particularly in relation with dose coverage of the duodenum, resulting in validation of 99% of plans.

Finally, altered fractionation regimens, particularly hypofractionated radiotherapy, may represent a promising area of investigation due to the possibility to deliver treatment in a shorter overall time, thus resulting in lower delay to surgery and improved integration with chemotherapy (Total Neoadjuvant Therapy, TNT). However, to our knowledge, only one prospective trial is exploring this possibility, using a moderate hypofractionated regimen (30 Gy in 10 fraction) followed by chemotherapy and surgery [https://doi.org/10.1200/JCO.2024.42.3_suppl.362].

*Conclusions*

In this review, limitations of historical chemoradiotherapy regimens in GC were examined in the light of modern clinical trials integrating modern surgical management and novel chemotherapy combinations. These treatments were delivered considering gastric cancer as a single disease. We need to include the molecular, histological and topographical differences in gastric cancer when developing new treatment strategies. Due to the disappointing outcome results and toxicity rates of both perioperative chemotherapy and adjuvant chemoradiotherapy, effort should be devoted in increasing the modest treatment completion rate without de-escalating treatment intensity. . A multidisciplinary team approach should manage the fragility of patients with gastric cancer to control their symptomatology enable treatment completion and maintain quality of life Anticipation of radiotherapy in the preoperative phase, use of modern radiotherapy techniques such as IMRT, harmonization of treatment volumes and investigation of altered fractionation dose regimens may represent a successful strategy to increase compliance, decrease treatment-related morbidity and maximize tumor response before surgery. Incorporation of immunotherapy, due to its potential synergy with radiotherapy, may be crucial to reduce the risk of distant dissemination that is currently the dominant pattern of relapse despite standard-of-care perioperative management. These hypotheses need to be urgently confirmed by prospective clinical trials.

Deleted: